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PRELIMINARY INVESTIGATION OF EFFECTS ON THE ENVIRONMENT OF BORON, INDIUM NICKEL, SELENIUM, TIN, VANADIUM AND THEIR COMPOUNDS

VOLUME III - NICKEL

VERSAR, INCORPORATED

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY

AUGUST 1975

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PRELIMINARY INVESTIGATION OF EFFECTS ON THE ENVIRONMENT OF BORON, INDIUM NICKEL, SELENIUM, TIN, VANADIUM AND THEIR COMPOUNDS

VOLUME III

NICKEL

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Volume III

Nickel

Contract No. 68-01-2215

Project Officer
Farley Fisher

Prepared for

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NICKEL

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Volume III

Preliminary Investigation of Effects on Environment of Nickel and Its Compounds

FOREWORD

This is Volume III of a series of six reports on the environmental effects of boron, indium, nickel, selenium, tin, and vanadium and their compounds. The information is based on literature reviews, direct contact with representatives of companies involved in the production or use of the materials, and consultation with knowledgeable individuals from industry, academic institutions and the Federal Government.

I. PRODUCERS, SITES, AND COSTS

A. Producers and Sites

Table 1 lists commercially significant chemical products and the companies involved. For this study significant is defined as production exceeding 1/2 kkg or $1,000 value per year. Other materials may also be included because of their unusual properties, such as toxicity, or their anticipated future significance.

Table 1
(1,2)

Chemicals, Producers and Plant Locations

	Producer	
Chemical	**Company and Subordination**	**Location**
Nickel (metal)	Ashland Chem. Co., Ind. Chems. and Solvents Div.	Dublin, Ohio
	Bram Metallurgical-Chem. Co.	Philadelphia, Pa.
	Chemetron Corp. Inorg. Chems. Div.	Cleveland, Ohio
	City Chem. Corp.	New York, N.Y.
	Electronic Space Products Inc.	Los Angeles, Cal.
	Kewanee Oil Co., Hanshaw Chem. Co.	Cleveland, Ohio
	Indussa Corp.	New York, N.Y.
	McKesson Chem. Co.	San Francisco, Cal.
	Pfizer Minerals, Pigments & Metals Div.	New York, N.Y.
	SEC Corp.	El Paso, Tex.
	United Minerals & Chem. Corp.	New York, N.Y.
	Ventron Corp., Alfa Products Div.	Beverly, Mass.
Nickel (powder)	Alcan Aluminum Corp., Alcan Metal Powders Div.	Elizabeth, N.J.
	Gallard-Schlesinger, Atomergic Chems. Co. Div.	Carle Place, N.Y.
	Bram Metallurgical-Chem. Co.	Philadelphia, Pa.

Table 1
(1,2)(cont.)

Chemical	Producer Company, subordination	 Location
Nickel (powder) (cont.)	Electronic Space Products Inc.	Los Angeles, Cal.
	SCM Corp., Glidden Metals, Glidden-Durkee Div.	Cleveland, Ohio
	Goldsmith, D.F. Chem. & Metal Corp.	Evanston, Ill.
	Var-Lac-Oid Chem. Co.	Elizabeth, N.J.
	Ventron Corp., Alfa Products Div.	Beverly, Mass.
Nickel acetate (Nickelous acetate)	C.P. Chems., Inc.	Sewaren, N.J.
	Filo Color and Chem. Corp.	Newark, N.J.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel acetylacetonate (Nickelous acetylacetonate)	MacKenzie Chem. Works, Inc.	Central Islip, N.Y.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel ammonium chloride (Nickelous ammonium chloride)	City Chem. Corp.	Jersey City, N.J.
Nickel ammonium sulfate (Nickelous ammonium sulfate)	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	Richardson-Merrell, Inc. J.T. Baker Chem. Co., subsid.	Phillipsburg, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel benzenesulfonate	City Chem. Corp.	Jersey City, N.J.

Table 1
(1,2)(cont.)

Chemical	Producer Company, subordination	Location
Nickel bromate	City Chem. Corp.	Jersey City, N.J.
Nickel bromide (Nickelous bromide)	City Chem. Corp.	Jersey City, N.J.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel caprylate (Nickelous caprylate)	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel carbonate (Nickelous carbonate)	American Can Co. M&T Chems., Inc., subsid.	East Chicago, Ind.
	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	C.P. Chems., Inc.	Sewaren, N.J.
	Kewanee Oil Co. Harshaw Chem. Co., Div. Indust. Chems. Dept.	Cleveland, Ohio
	PVO Internat'l, Inc.	Boonton, N.J.
	Richardson-Merrell, Inc. J.T. Baker Chem. Co., subsid.	Phillipsburg, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel carbonyl	Pressure Chem. Co.	Pittsburgh, Pa.
Nickel chloride (Nickelous chloride)	Allied Chem. Corp. Specialty Chems. Div.	Marcus Hook, Pa.
	American Can Co. M&T Chems. Inc., subsid.	East Chicago, Ind. Pico Rivera, Cal.
	Associated Metals & Minerals Corp. Gulf Chem. Metallurgical Co., div.	Texas City, Tex.

Table 1
(1,2)(cont.)

Chemical	Producer	
	Company, subordination	Location
Nickel chloride (cont.)	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	C.P. Chems., Inc.	Sewaren, N.J.
	Filo Color and Chem. Corp.	Newark, N.J.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	Mallinckrodt Chem. Works Indust. Chems. Div.	St. Louis, Mo.
	Pearsall Chem. Corp.	La Porte, Tex.
	Richardson-Merrell, Inc. J.T. Baker Chem. Co., subsid.	Phillipsburg, N.J.
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel chromate	City Chem. Corp.	Jersey City, N.J.
Nickel citrate	City Chem. Corp.	Jersey City, N.J.
Nickel cyanide	City Chem. Corp.	Jersey City, N.J.
Nickel dimethylglyoxime	City Chem. Corp.	Jersey City, N.J.
Nickel 2-ethylhexanoate (Nickelous octanoate)	Mooney Chems., Inc.	Franklin, Pa.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel ethyl sulfate	City Chem. Corp.	Jersey City, N.J.

Table 1
(1,2)(cont.)

Chemical	Producer Company, subordination	 Location
Nickel fluoborate (Nickelous fluoborate)	Allied Chem. Corp. Specialty Chems. Div.	Marcus Hook, Pa.
	American Can Co. M&T Chems. Inc., subsid.	East Chicago, Ind.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	Ozark-Mahoning Co.	Tulsa, Okla.
	Ventron Corp., Alfa Products Div.	Beverly, Mass.
Nickel fluoride	Allied Chem. Corp. Specialty Chems. Div.	Marcus Hook, Pa.
	American Can Co. M&T Chems. Inc., subsid.	East Chicago, Ind.
	Ozark-Mahoning Co.	Tulsa, Okla.
Nickel formate (Nickelous formate)	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	Filo Color and Chem. Corp.	Newark, N.J.
	PVO Internat'l, Inc.	Boonton, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel halide	Ventron Corp., Alfa Products Div.	Beverly, Mass.
Nickel hexamine fluoborate (Hexammino-nickel fluoborate)	Ventron Corp., Alfa Products Div.	Beverly, Mass.

Table 1
(1,2) (cont.)

Chemical	Producer Company, subordination	Location
Nickel hydrate	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	PVO Internat'l, Inc.	Boonton, N.J.
Nickel hydroxide (Nickelous hydroxide)	Filo Color and Chem. Corp.	Newark, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel iodide (Nickelous iodide)	City Chem. Corp.	Jersey City, N.J.
Nickel metasilicate	City Chem. Corp.	Jersey City, N.J.
Nickel naphthenate (Nickelous naphthenate)	The Shepherd Chem. Co.	Cincinnati, Ohio
	Troy Chem. Corp.	Newark, N.J.
Nickel neodecanoate (Nickelous neodecanoate)	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel nitrate (Nickelous nitrate)	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	Filo Color and Chem. Corp.	Newark, N.J.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	Mallinckrodt Chem. Works Indust. Chems. Div.	St. Louis, Mo.
	Richardson-Merrell, Inc. J.T. Baker Chem. co., subsid.	Phillipsburg, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Long Beach, Cal. Elizabeth, N.J.

Table 1
(1,2) (cont.)

Chemical	Producer: Company, subordination	Producer: Location
Nickel octoate (See: Nickel 2-ethylhexoate)		
Nickel oxide (Nickelous oxide) (Nickelous oxide, green)	Richardson-Merrell, Inc. J.T. Baker Chem. Co., subsid.	Phillipsburg, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel oxide, black (Nickelic oxide) (Nickel peroxide) (Nickel sesquioxide)	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
Nickel phosphate (Nickelous phosphate) (Trinickelous orthophosphate)	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel potassium chromate (Nickelous potassium chromate) (Potassium nickel chromate)	City Chem. Corp.	Jersey City, N.J.
Nickel potassium cyanide (Nickelous potassium cyanide)	City Chem. Corp.	Jersey City, N.J.
Nickel potassium fluoride (Potassium nickel fluoride)	Allied Chem. Corp. Specialty Chems. Div.	Marcus Hook, Pa.
	City Chem. Corp.	Jersey City, N.J.
Nickel potassium sulfate (Potassium nickel sulfate)	City Chem. Corp.	Jersey City, N.J.

Table 1
(1,2)(cont.)

Chemical	Producer	
	Company, subordination	Location
Nickel propionate (Nickelous propionate)	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel sesquioxide (See: Nickel oxide, black)		
Nickel silicofluoride (Nickelous silicofluoride)	City Chem. Corp.	Jersey City, N.J.
Nickel stannate	American Can Co. M&T Chems. Inc., subsid.	Carrollton, Ky.
Nickel stearate (Nickelous stearate)	The Norac Co., Inc. Mathe Chem. Co., div.	Lodi, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Witco Chem. Corp. Organics Div.	Clearing, Ill. Los Angeles, Cal. Perth Amboy, N.J.
Nickel sulfamate	American Can Co. M&T Chems. Inc., subsid.	East Chicago, Ind. Pico Rivera, Cal.
	City Chem. Corp.	Jersey City, N.J.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel sulfate (Nickelous sulfate)(Nickel salts, single)	American Can Co. M&T Chems. Inc., subsid.	East Chicago, Ind. Pico Rivera, Cal.

Table 1
(1,2)(cont.)

Chemical	Producer Company, subordination	Location
Nickel sulfate (cont.)	Associated Metals & Minerals Corp. Gulf Chem. & Metallurgical Co., Div.	Texas City, Tex.
	Chemetron Corp. Chems. Group Inorganic Chems. Div.	Cleveland, Ohio
	C.P. Chems., Inc.	Sewaren, N.J.
	Filo Color and Chem. Corp.	Newark, N.J.
	Harstan Chem. Corp.	Brooklyn, N.Y.
	Kennecott Copper Corp. Metal Mining Div. Utah Copper Div.	Salt Lake City, Ut.
	Kewanee Oil Co. Harshaw Chem. Co., div. Indust. Chems. Dept.	Cleveland, Ohio
	Mallinckrodt Chem. Works Indust. Chems. Div.	St. Louis, Mo.
	Phelps Dodge Corp. Phelps Dodge Refining Corp., subsid.	Maspeth, N.Y.
	PVO Internat'l, Inc.	Boonton, N.J.
	Richardson-Merrell, Inc. J.T. Baker Chem. Co., subsid.	Phillipsburg, N.J.
	The Shepherd Chem. Co.	Cincinnati, Ohio
	Tenneco Inc. Tenneco Chems., Inc. Intermediates Div.	Elizabeth, N.J. Long Beach, Cal.
Nickel sulfide	City Chem. Corp.	Jersey City, N.J.
Nickel sulfite	City Chem. Corp.	Jersey City, N.J.
Nickel thiocyanate	City Chem. Corp.	Jersey City, N.J.

Table 1
(1,2)(cont.)

Chemical	Producer Company, subordination	 Location
Nickel titanate (Nickelous titanate)	N L Indust., Inc. TAM Div.	Niagara Falls, N.Y.
	The Shepherd Chem. Co.	Cincinnati, Ohio
Nickel zirconate	N L Indust., Inc. TAM Div.	Niagara Falls, N.Y.
Nickel alloys	Atomergic Chemetals Co., Gallard Schlesinger Mfg. Co.	Carle Place, N.Y.
	Bram Metallurgical-Chem. Co.	Philadelphia, Pa.
	Electronic Space Products, Inc.	Los Angeles, Cal.
	Engelhard Minerals & Chem. Corp.	Murray Hill, N.J.
	Glidden Metals, Glidden-Durkee Div., SCM Corp.	Cleveland, Ohio
	Hanna Mining Co.*	Riddle, Oregon
	Pfizer Minerals, Pigments & Metals Div.	New York, N.Y.
	United Mineral & Chem. Corp.	New York, N.Y.
	Ventron Corp., Alfa Products Div.	Beverly, Mass.

*Produces ferronickel (approximately 50% nickel-50% iron) which commercially and for tax purposes is considered as primary nickel.

B. Prices

The producers' price for electrolytic nickel was raised from $2.93 to $3.37 per kilogram in September, 1972. The price of domestic ferronickel was $2.83 per kilogram until December, 1973, when it was raised to $3.05 per kilogram.(3)

C. Physical Properties

Physical properties of nickel metal and nickel compounds are presented in Table 2.

Table 2
(4)

Physical Properties

Chemical	Specific Gravity	Melting Point °C	Boiling Point °C	Solubility Water g/100cc
Nickel	8.90	1453	2732	i
Nickel sulfate	3.68	d848^{760}		29.3^{0}, 83.7^{100}
Nickel chloride	3.55	1001	subl 973	64.2^{20}, 87.6^{100}
Nickel carbonyl	1.32	-25	43	0.018$^{9.8}$

II. PRODUCTION

A. Quantities

In 1972 the Hanna Mining Company at Riddle, Oregon, was the sole producer of primary nickel from domestic nickel ore. Primary nickel was a by-product in the refining of other metals. In addition, nickel, either as metal, alloy, or chemical compound, was recovered from nonferrous scrap. Table 3 shows the domestic supply of nickel in 1972. In 1972, 157,500 metric tons of nickel were imported, over three times the amount produced domestically.(3)

Table 3

1972 Domestic Nickel Production, metric tons nickel

From domestic ore-	11,998
By-product of metal refining-	2,273
Recovered from nonferrous scrap-	32,592
Total	46,863

Disposal of the nickel held in the national stockpile was authorized on July 26, 1972. None, however, reached the open market during the year.(3)

B. Process for Nickel Production

The entire domestic production of nickel ore comes from an open-pit mine near Riddle, Oregon. The ore is approximately 1.4 per cent nickel. It is extracted from the mountain and transported about two thousand feet to the smelter where it is melted in electric furnaces and poured into reaction ladles. In the ladles the melted ore is reduced by the addition of crushed ferrosilicon to the molten ferronickel.

C. Nickel Carbonyl Process (Nickel Recovery and Refining)

This process produces high purity nickel in powder form. During the Manhattan Project of World War II, the product from this process was a key factor in the gaseous diffusion barrier used in the separation of uranium-235. Although this process is still widely used, the compound nickel carbonyl is an intermediate and is usually a captive material. Only one company is listed in Table 1 as offering the compound for sale.

In the nickel carbonyl process, nickel and carbon monoxide are heated to form nickel carbonyl which, when heated, reverts back to nickel and carbon monoxide. Pressures of the order of 20 atmospheres and temperatures of about 150C are used for the decomposition.(5)

D. Nickel Sulfate

1. Nickel sulfate is produced from two different raw materials, pure nickel or nickel oxide or spent nickel plating solutions. With the first case the metal or oxide is digested in sulfuric acid, filtered, and either packaged for sale or processed to recover the solid hexahydrate. The sludges recovered by filtration can be further processed to produce more nickel sulfate.(6)

2. When spent nickel plating solution is the raw material, the first step is also treatment with sulfuric acid. The resulting solution has to be treated sequentially with oxidizers, lime, and sulfides to precipitate impurities. The solution is filtered and marketed or else further processed to provide a solid product. To recover a solid product from either process, the nickel sulfate solutions are first concentrated, filtered, and fed to a crystallizer. The resulting suspensions are fed to a classifier and the solid product recovered. This is then dried, cooled, screened, and packaged for sale. The recovered solids from the filtration step and mother liquor from the classifiers are recycled to an earlier part of the process.(6)

III. USES

A. New and Old Nickel Scrap

Table 4
(3)

1972 Consumption, metric tons nickel

New and Old Scrap

Consumer	Type of Scrap New	Old	Total
Smelters and Refiners:			
Nickel and nickel alloys	661	5,936	6,597
Monel Metal	554	2,094	2,648
Nickel silver*	739	1,875	2,615
Cupronickel*	----	476	476
Nickel residues	4,990	----	4,990
Total	6,205	8,030	14,235
Foundries and Plants of Other Manufacturers:			
Nickel and nickel alloys	1	25,341	25,342
Monel metal	9	123	132
Nickel silver*	10,877	----	10,877
Cupronickel*	14,624	91	14,715
Nickel residues	-----	141	141
Total	10	25,605	25,615
Grand Total			
Nickel and nickel alloys	662	31,277	31,939
Monel metal	563	2,217	2,781
Nickel silver*	11,617	1,875	13,492
Cupronickel*	14,624	567	15,191
Nickel residues	4,990	141	5,131
Total	6,215	33,635	39,851

*Excluded from totals because it is copper-base scrap, although containing considerable nickel.

B. Nickel

Table 5
(3)

1972 Consumption of Nickel (Exclusive of Scrap) by Use and Form (Metric tons)

Use	Commercially Pure Unwrought Nickel	Ferro-Nickel	Nickel Oxide	Nickel Sulfate and Other Salts	Other Forms	Total of Figures Shown
Steel:						
Stainless & heat resisting	15,563	15,230	10,157	------	206	41,065
Alloy(excludes stainless)	7,194	4,540	5,813	------	193	17,559
Superalloys	10,465	228	44	------	396	11,133
Ni-Ca alloys	7,536		33	------	181	7,749
Permanent magnet alloys	3,561	200	49	------		3,810
Other Ni-alloys	25,286	244	633	5	44	26,212
Cast Irons	2,563	247	364		851	4,024
Electroplating[1]	22,998	-------	28	3,218	97	26,341
Chemical Uses	822	-------	64	185		1,071
Other Uses[2]	4,186	1	337	166	576	5,265
Total reported and estimated	100,154	20,690	17,522	3,574	2,544	144,229

[1] Based on monthly estimated sales to platers.

[2] Includes batteries, catalysts, ceramics, and other alloys containing nickel.

C. Table of Uses

Table 6
(7,8,9)

Nickel Compound	Use	Purpose	Comments
Nickel	Alloying Element	Used for corrosive-resistant steels and special property alloys	
Nickel Carbonyl	Mond Process	Intermediate in refining nickel	"Mond" nickel used for metallic mirrors and to coat objects
	Catalyst	Used in the carbonylation reaction, i.e., reaction of olefins, acetylene, haloacetylenes, alcohols, and anyl halides with carbon monoxide	
	Other	Powder metallurgy	Nickel powder can be produced by the controlled decomposition of nickel carbonyl
Nickel Sulfate	Nickel-plating		
	Mordant	Used for dyeing and printing fabrics, coloring metals, ceramics, and for producing driers for use in protective coatings	
	Other	Food additive	Permitted in the feed and drinking water of animals, and for treating food producing animals. Also permitted in food for human consumption
Nickel Chloride	Nickel-plating		
	Antiseptic		
	Gas Masks	Absorbent for ammonia	

D. Substitute Materials

The use of nickel in alloy systems, especially alloy steels, constitutes the bulk of the demand. The specific properties sought vary with the different alloys, but the major features are toughness, corrosion resistance, hardness, and strength. There are other ways of obtaining these properties such as substituting chromium or molybdenum as alloy ingredients or by the use of a coating. One could also tolerate a slightly inferior product. Nickel, however, appears to be more economical than the substitutes. Also the available supply of nickel in the United States is adequate. This has not always been true because of worldwide imbalance between supply and demand. During a period of nickel shortage, aluminum began replacing stainless trim. This trend is still continuing.(10)

IV. CURRENT PRACTICE

A. Transportation and Handling Regulations

1. Nickel powder or finely divided nickel, also nickel catalyst, activated or spent, are classified as flammable solids. The Interstate Commerce Commission requires a yellow label on shipping containers and limits loads to 45 kilograms. These are not accepted for transport by air unless mixed with 40 per cent water or some other suitable liquid. Air transport containers require a yellow label.(9)

2. Nickel carbonyl is classified as a flammable liquid by the ICC and is not accepted for transport by land or air. This compound is given the highest "Toxic Hazard Rating."(9)

3. No special transportation and handling regulations exist for other nickel compounds with the exception of nickel cyanide.(9)

V. ENVIRONMENTAL CONTAMINATION

A. From Use

The principal use of nickel is as an alloying element. For purposes of this application, the metal or the composition used is insoluble and unlikely to escape into the environment except by emission to the atmosphere. At the high temperatures involved in the melting and alloying of the various steel alloys, non-ferrous alloys, special electrical resistance alloys, and cast iron, the emissions to the atmosphere are in the form of nickel oxide or a complex oxide involving other alloying elements. Nickel emission factors for these various operations were obtained from manufactures and together with the 1968 emissions are presented in Table 7.(11)

Table 7
(11)

1968 Nickel Emissions to the Atmosphere

Product	Nickel Emission Factor, kg/metric ton Nickel Charged	Emissions, metric tons
Nickel alloys	2	48
Cast iron	20	72
Copper-base alloys	2	5
Electrical Resistance alloys	2	5
Alloy steels	10	130

The use of nickel or its compounds in electroplating is a potential source for environmental contamination of the waters with soluble nickel salts. The plating solutions normally used contain nickel sulfate or nickel chloride. According to a survey conducted by Battelle in 1965, the estimated daily raw waste from nickel plating amounted to 54,430 kilograms per day of these nickel salts. Also, only 17 per cent of the total nickel salts used was consumed by plating. In addition to particles of the plating solution, raw waste may contain small concentrations of other heavy metals, depending on the kind of material being processed. Leakage from filters, pipes, and pumps is a secondary source of nickel wastes. The relatively high value of nickel has encouraged the adoption of process controls for minimizing losses into the rinse water after the plating. Also because of their relatively high value, nickel plating baths are rarely dumped.(12)

B. From Production

The ecological consequences of heavy metal damage are probably masked by the damage caused by sulfur dioxide emitted by the metal smelters. In the case of the smelter at Sudbury, Canada, east and south of the smelters, soil and vegetation, plant leaves, dust, and rainfall were sampled and analyzed. Elevated levels of nickel was detected up to 50 kilometers from the smelters and toxic water levels extended to 15 kilometers. The soil contamination had a pattern indicative of an airborne smelter source. Nickel levels were 2835 ppm at 0.8 kilometers, 1522 ppm at 5.5-8 kilometers, 306 ppm at 20 kilometers and 83 ppm at 50 kilometers from the source. Average soil levels were 40 ppm for nickel.(13)

Nickel ions (+2,+3) may be present in significant amounts in the waste water from the manufacture of nickel sulfate.(6) This is of concern because of its toxicity to aquatic organisms at certain concentrations.(14)

Workers in plants for the electrolytic refining of nickel contracted diseases of the upper respiratory passage as a consequence of the inhalation of air containing nickel chloride and nickel sulfate. Nickel production using the Mond process involves the use as an intermediate of nickel carbonyl, which is an extremely toxic material.(15)

C. From Inadvertent Sources

1. Combustion of oil

Nickel is present in most crude oils and remains in the residuals after the crude oil is refined. The residual fuel oil burned by utilities and for commercial heating contains essentially the same amount of nickel as was present in the crude. The amount varies widely for domestic and imported crude oils. The extremes for eleven sources of domestic crude were 1.4 to 64.0 ppm nickel, for 24 imported crudes from 0.3 to 29.5 ppm nickel. For the most part controls are not used in oil-fired units. Assuming an average nickel content of ten ppm, the emissions to the atmosphere for 1968 from the combustion of residual fuel oil was estimated at 4,509 metric tons of nickel.

2. Combustion of coal

The emissions from a coal-fired power plant were collected and analyzed. The nickel concentrations found in the fly ash ranged from 1.3 to 7.0 x 10^{-4} grams per cubic meter. Based on 272,000,000 metric tons of coal consumed by power plants in 1968, 75 per cent particulate control, nickel concentration of 1.3 x 10^{-4} grams per cubic meter, the nickel emissions were 90 metric tons.

3. Incidental formation of nickel carbonyl

Nickel carbonyl is formed from a reaction between nickel and hot carbon monoxide probably in incinerators where nickel is found in sewage sludge or solid waste.(16) This could occur in internal combustion engines if an additive containing nickel was used. Such additives are banned in the United States and should not be permitted in the future.

D. Total Nickel Emissions

Nickel release to the environment in the United States from various sources on a yearly basis is estimated below. Most of the values are based on 1968 figures or estimations.

Table 8

Nickel Emission

Source	Total Nickel Emission (kkg/yr)	Year	Comments
Product Use	260	1968	Atmosphere, waters
Fuel Oil Combustion	4,509	1968	Atmosphere
Coal Combustion	90	1968	Atmosphere
Nickel Sulfate Manufacture	1	1971	Only from spent plating baths as raw material-into waters
Wastes from Nickel Electroplating	15	1971	Based on data from Effluent Guidelines Development Document EPA-440/1-73-003 (1973)
Phosphate Rock Mining	5	1972	Based on 30 ppm Ni; to landfill
Other Mineral and Ore Mining	10	Current	Estimated; primarily to land and water
Miscellaneous	5	Current	Estimated
Total	4,895		Mostly from oil combustion and emitted to atmosphere as oxides

VI. MONITORING AND ANALYSIS

A. Monitoring

The last extensive survey of the air quality over the United States was conducted in 1968-1969 by the Quality Assurance and Environmental Monitoring Laboratory of the National Environmental Research Center, in Research Triangle Park, with the assistance and cooperation of state and local agencies. Among the data compiled by the National Air Surveillance Networks of the U.S. Environmental Protection Agency were the concentrations of nickel particulates over urban and nonurban regions for various seasons. The maximum value reported was 1.30 $\mu g/m^3$ for Portland, Maine. The nickel concentrations were considerably lower for nonurban vs. urban areas.(17) There was a greater concentration of nickel in the air over urban vs. nonurban areas. This is a direct result of greater urban industrialization.

Nickel concentration appeared to be greater in the first and fourth quarters of the year (the colder months) than in the second and third quarters. Presumably this could reflect the use of coal and oil for heating.

B. Analysis

1. Nickel carbonyl

Infrared spectrophotometry using multiple-reflection long-path cells was used in the quantative analysis of nickel carbonyl vapors. By using the very strong carbonyl stretching frequencies near 2,000/cm, detectability limits on the order of 0.01-0.001 ppm were attained. The method is rapid, specific, and free from interference. Accuracy is estimated at ± 10 per cent.(18)

The American Industrial Hygiene Association indicates that a direct field instrument is commercially available for continuous monitoring of operations involving nickel carbonyl. The instrument can be used over a range of 10 ppb to 1,500 ppb.(19)

Investigations to find a granulated chemical sorbent for the efficient absorption of nickel carbonyl at high rates of air passage were conducted. Of all the chemical sorbents investigated, The best results were given by finely porous silica gel with grain size 0.25-0.5 mm. impregnated with a solution of potassium iodate in sulfuric acid. To prepare the sorbent the silica gel was purified by boiling with diluted hydrochloric acid (1:1), washed with hot water to a negative reaction to chloride, dried at 200C and ignited for 30 minutes at 600C. On cooling, the silica gel was impregnated with five per cent solution of potassium iodate in ten per cent solution (by weight) sulfuric acid, using one volume of the iodate per three volumes powder. The impregnated silica gel was distributed in a thin layer in a porcelain dish, heated at 180C for two hours and then transferred, while still hot, to a flask with a tight fitting ground-glass stopper. The sorbent prepared was used to fill beaded glass tubes. It was found that with three ml. sorbent, the air alloy should be sampled at the rate of 15 cu. m./min. The loss of nickel carbonyl did not exceed 1.5% even at comparatively high concentrations of the substance. The method makes possible the determination of thousandths of a milligram of nickel carbonyl in a cu. m. air, by sampling 0.5 cu. m. air in 30 minutes.(20)

2. Nickel in particulates

To detect nickel in airborne contaminants collected in air filters a small portion of the filter is rolled up into a cylinder and placed in a hollow graphite electrode. This portion of the air filter is directly excited by the condensed spark discharge in an oxygen atmosphere. The sample burns, exciting the spectra. A photographic recording is used to interpret the spectra and, when improved precision is required, line intensities are measured with a microphotometer. The limits of detection are 0.1 to 1.0 micrograms. The results obtained from the rapid emission spectrographic method are compatible with results obtained with the more conventional technique of ashing the filter, mixing it with a spectrographic buffer, and exciting it in a D.C. arc.(21)

VII. CHEMICAL REACTIVITY

A. Environmental and Use Associated Reactions

Nickel air pollution usually stems from particulate emissions from burning coal, oil, or incinerators of nickel-containing material and is normally an oxide. This can be controlled with the usual dust handling equipment such as bag filters, precipitators, and scrubbers. When the pollutant is gaseous nickel carbonyl, it can be passed through a furnace and decomposed into nickel and carbon monoxide. Nickel carbonyl is reportedly formed when hot carbon monoxide is passed over nickel. This can occur in the burning of solid wastes containing nickel(15) or in cigarette smoke.(22)

1. Effect of nickel on activated sludge and anaerobic digestion processes

Studies were made to determine the nickel tolerance of the activated sludge process and its related capacity to remove nickel from sewage. Significant but modest adverse effects on biological and chemical oxygen demands, suspended solids, and turbidity were noted at 2.5 ppm nickel. Digestion of primary and activated sludge was not impaired at influent concentrations as high as 40 ppm. Treatment removed 30 per cent of the influent nickel.(23)

VIII. BIOLOGY

A. Absorption, Distribution, Excretion

1. Humans

a. Normal levels in healthy individuals

Nickel occurs in two forms in the blood: a so-called ultrafiltrable fraction and a protein bound fraction, which together account for 87 to 89 per cent of the nickel in man.(24)

Various levels for normal serum nickel concentrations have been reported as shown in Table 9.

Table 9. Normal Serum Nickel Levels

Total Serum Ni (ug/l)	Method of Analysis	Reference
3.05 ± 0.15		(25)
2.3	A A S	(26)
2.6 ± 0.8	A A S	(27)
0.78	emission spectrophotometry	(28)
3.3 - 142.7		(29)
2.2	uv spectrophotometry	(30)
2.6 ± 0.8		(31)
1.52 ± 0.05		(32)

Measurements of nickel in fractions of human serum proteins prepared by electrophoresis and by cold-ethanol precipitation revealed the highest concentrations of nickel in the serum beta-globulins. Mean urine nickel concentration from 17 normal humans, determined by atomic absorption spectrophotometry after a dimethylglyoxime extraction to concentrate the nickel was 1.8 μg ± 0.8 μg per 100 ml or 1.98 μg ± 1.0 per 24 hours.(33)

Wavelike variations in nickel content in the blood of healthy children, ages 8 to 14 years, were found to be unrelated to age or sex.(34)

Nickel was found in only a few samples of palatine tonsils removed from thirty-six patients.(35)

b. In Disease States

Attempts have been made to correlate nickel levels with various disease states. Levels of nickel found in the patients of one hospital are shown in Table 10.(27)

Table 10.

Serum Nickel Levels in Hospital Patients with Various Conditions

Condition	Hrs. After Onset	Serum Ni (µg/l) ± S.D. (n)	
healthy		2.6 ± 0.8 (47)	
acute myocardial infarction	13-36	5.2 ± 2.8 (33)	(P<0.0001)
acute stroke	37-72	4.5 (12)	(P<0.005)
acute burns (<25% of body)	37-72	7.2 (3)	(Range = 4.1-10.9)
hepatic cirrhosis		1.6 ± 0.8 (18)	(P<0.005)
chronic uremia		1.7 ± 0.7 (12)	(P<0.005)
acute myocardial ischemia without infarction	13-36	3.3 ± 1.6 (22)	
acute trauma with bone fractures	13-36	2.7 ± 0.9 (19)	
acute delirium tremens	13-36	2.3 ± 0.9 (25)	
muscular dystrophy		2.3 ± 1.4 (10)	
immediate postpartum mothers		3.0 ± 1.3 (12)	
umbilical cord		3.0 ± 1.2 (12)	

Changes in levels of trace elements in patients during stenocardia attack may reflect an increase in the tone of the sympathetic nervous system.(36) Heparinized blood from 146 patients with chronic pneumonia was analyzed for nickel. An increase in nickel was found in patients with the asthmatic component. but not if the pneumonia was complicated by respiratory insufficiency. A direct correlation between serum nickel and beta-globulin was observed.(32) In humans with rheumatoid arthritis, increases in serum nickel and copper were observed, depending upon the activity of the disease.(37)

A substantial increase in nickel in the blood of patients with radiation dermatitis has been reported.(38)

In patients suffering from endemic fluorosis in the Apsheron peninsula in the USSR, an increase in the concentration of nickel in the blood occurs.(39) Depending on the type of development and clinical forms of the disease, the nickel content in the blood and cerebrospinal fluid increased in patients exhibiting a continuous course of schizophrenia. Nickel increased in the blood and cerebrospinal fluid of patients with simple, hebephrenic, paranoid forms and lucid catatonia, but the increase was even greater in patients with acute Kandinsky syndrome, depressive paranoid schizophrenia and oneiroid catatonia. Brain, liver, muscle and spleen nickel levels were lower in schizophrenics than in normals, but schizophrenics had elevated nickel levels in the kidney, lung and adrenals.(40) A pronounced drop in blood nickel levels occurred in patients with the beginning stages of rickets. This decrease occurred prior to the development of anemia.(41)

Significant changes in serum nickel concentrations have been observed in some children with leukemia:

Condition	Nickel in Blood (µg %)
healthy	18 (7.5-40)
leukemic	12.5 (2.5-45)
anemic leukemic	7.7

No changes in nickel concentration occurred after treatment even when the patient's condition improved.(42) Changes in the nickel content of the bones have also been reported in children with leukemia.(43) Increases in nickel, zinc, copper and manganese occurred in the bone marrow and peripheral blood cells in 34 patients with various leukemias.(44) The nickel content in the spleens and livers of 41 patients who died from leukemia was lower than normal. The most severe decreases occurred in victims of chronic leukemia. Less severe decrements were found in acute leukemia victims.(44) The normal range of nickel, 3.3 to 142.7 micrograms per liter, in human serum was not altered by leukemia.(45)

Electron microprobe analysis of trace elements in normal and malignant human tissue revealed extremely high concentration of nickel, copper, zinc, calcium, titanium, chromium and iron. The frequency of occurrence of these metals appeared to be greater in malignant tissue.(46) Nickel concentrations were normal in patients with cancer and precancerous condition of the uterine cervix; however, manganese was low, and chromium, high.(47)

Mean serum nickel doubled in victims of acute myocardial infarction 12 to 36 hours after the onset of the attack, reaching a level of 5.4 ± 2.7 µg/l as compared with an average control value of 2.6 ± 0.8 µg/l based on 40 healthy controls. Elevated serum nickel was observed in 72 per cent of the patients with infarctions ($P < 0.0005$). No significant change in mean serum nickel concentration occurred in 17 patients with acute myocardial ischemia without infarction, or in 132 other hospital patients with noncardiac diseases.

Nickel binding and absorption by human skin has been studied using cadavers. The corneal epidermis prevented nickel sulfate penetration, but the Malphigian layer, dermis and hypodermis were easily penetrable.(48) Nickel (II) ions are bound by the dermis of cadaver skin as measured by changes in dermis potential, swelling and absorption. The binding is reversible, but is stronger than would be expected due to electrostatic forces alone. Nickel ions are especially strongly bound at low concentrations.(49) Organic solvents rubbed into skin of the plantar arch did not facilitate nickel penetration except as the solvent was able to cause damage to the thickness of the keratin layer. Nickel was observed only in the external part of the keratin layer.(50)

Fecal excretion of nickel by healthy humans without occupational exposure to nickel averaged 3.3 micrograms per gram wet weight (2.1 - 4.4 μg/gm), compared with a value for occupationally exposed workers of 14.2 micrograms per gram dry weight, (10.8 - 18.7 μg/g) or 258 micrograms per day (80 - 540 μg/day).(51) Normal, unexposed adults excreted 0.027 micrograms nickel per ml of urine. Workers in a nickel smelting plant, where the mean nickel concentration in the air was 0.349 micrograms per liter, had an average urinary nickel concentration of 0.240 micrograms per ml.(52) Individuals known to be ingesting 41.5 - 77.7 μg nickel in the daily diet, 7.08 to 22.1 μg (17.0 to 28.4%) was excreted in the urine, and 8.8 to 54.1 μg (21.2 to 69.6%) was excreted in the feces.(45) In adolescents, a sensitive balance between nickel and cobalt has been described. If the diet contains 30-33 μg of cobalt per day and 280 - 310 μg of nickel, the minimum daily requirements are almost completely filled. The cobalt:nickel ratio in the urine is twice that in the feces and diet. The amount of nickel excreted in the urine was 10.6% of the amount ingested (22.6% for cobalt), and the rest was excreted in the feces.(53)

Kidney excretion of nickel was largely independent of kidney hemodynamic values. Large individual variation is observed. In an experiment examing the effects of various states of diuresis on nickel excretion, the results shown in Table 11 were obtained:(54)

Table 11

Effects of Various States of Diuresis
on Urinary Nickel Excretion (54)

Condition	Urine Flow (ml/min)	Ni Excretion (ng Ni/min)	Ni Excretion (ng Ni/ml urine)
Antidiuretic healthy & kidney patients	1.08 ± 0.72	4.27 ± 4.79	3.95 ± 4.43
Diuresis	4.43 ± 2.11	29.7 ± 31.2	6.70 ± 7.04
Osmotic diuresis	23.5 ± 7.2	84.2 ± 94.9	3.58 ± 4.03

The concentration of nickel excreted in the scales of patients with psoriasis was found to exceed that in normal desquamation.(55) Humans suffering from chronic gastritis or stomach cancer have reduced serum nickel levels due to disturbed resorption and excretion of microelements in the digestive tract.(56)

2. Mammals

Serum levels of total and ultrafiltrable nickel have been determined by atomic absorption spectrometry for several species.(57) In an equilibrium dialysis study, *in vitro* binding of nickel-63 (II) to serum albumin of several species was determined, and the first association constants were calculated.(58) This data is summarized in Table 12.

Table 12

Bound and Ultrafiltrable
Serum Nickel in Various Species (58)

Species	Total Serum Ni (μg/l)	% Ultrafiltrable Ni	63% Ni (II) bound *in vitro*	First association constant
man	2.3	41	87-89	3×10^5
rat	6.6	27	87-89	2×10^5
rabbit	9.0	16	87-89	$>3 \times 10^5$
dog	2.3	>85	55	2.5×10^4
pig	---	--	75	8×10^4
lobster	8.8	38	—	———

The species differences in the ability of serum albumin to bind nickel account for differences in amounts of ultrafiltrable nickel.(24)

The mean concentration of nickel in the ultracentrifugal supernatant of homogenates of rat lung and rat liver were determined to be:(33)

Organ	µg Ni/gm RNA (Range)
lung	48 (34-64)
liver	29 (21-39)

Serum nickel levels in cows suffering from lymphoid leukemia were 1.5 to 2 times the levels of normal animals.(59)

No change in serum nickel or nickel in affected skin areas was observed in rabbits with radiation dermatitis.

Rubbing the skin of the abdominal wall of the guinea pig with various organic solvents and nickel sulfate for ten minutes resulted in absorption of nickel, which was detected in the skin, kidneys and liver.(50) Nickel was not absorbed from compresses of nickel sulfate applied to rabbit skin unless skin lesions were present.(53)

Calves fed rations containing 62.5, 250 or 1000 ppm nickel as nickel carbonate actually ingested 0.4, 1.3 and 1.6 gm nickel per day. As a result, a significant increase in the nickel concentration in many tissues occurred in the group ingesting 1000 ppm nickel rations. The order of tissue accumulation was serum>kidney>vitreous humor>lung>testis>bile>tongue>pancreas>rib>spleen>brain. Liver and heart levels were not significantly different from controls. Of the total nickel excreted, 97.1% was excreted in the feces.(61) No change in milk production, composition, nickel content, animal health, or feeding habits occurred in lactating dairy cows fed diets containing 0, 50 or 250 ppm nickel as nickel carbonate.(62)

In rats subjected to nickel carbonyl inhalation, nickel carbonyl was detected in the blood stream. In rats injected with nickel carbonyl, the intact compound was found in the expired breath revealing that nickel carbonyl can cross the aleveolar membranes in both directions.(63)

Subcellular nickel distribution is such that nickel is principally located in the lung and liver microsomes and supernatant. After acute and chronic inhalation exposures to nickel carbonyl, nickel was elevated in these fractions. Chronic exposures resulted in nickel elevation in the nuclear and mitochondrial fractions as well.(64)

The distribution of nickel-63 carbonyl, either injected into or inhaled by rats, was determined at various times after treatment. After one hour, 48 per cent of the nickel-63 in the blood was contained in the red blood cells, but only 8 per cent remained in the erythrocytes after six hours, when most of the nickel in the blood was bound to serum albumin. Thirty-eight per cent of the nickel-63 dose was expired in the breath during the first six hours after treatment. During the four days following exposure, 31 per cent of the nickel-63 was excreted in the urine, but only two per cent in the feces. Twenty-four hours after exposure, nickel-63 was found in DNA, RNA and protein of lung and liver homogenates, and was distributed throughout the nuclear, mitochondrial, microsomal and supernatant fractions in proportion to their dry weights.(65)

A significant correlation between blood volume and nickel-63 content of organs was observed in rats injected intravenously with nickel-63 at 15 minutes, 2, 6 and 16 hours after injection. Sixty-one per cent of a single injection appeared in the urine and 5.9% in the feces after 72 hours. Nickel-63 activity had disappeared from whole blood by 48 hours after injection. The relative distribution of the remaining nickel was: kidney>adrenal>ovary>lung>heart>eye>thymus>pancreas>spleen>liver>epidermis>GI tract>muscle>incisor>femur = brain>adipose tissue. The nickel-63 decreased rapidly in all tissues, and only the kidney contained significant amounts after 72 hours.(66)

In rabbits injected intravenously with 0.24 mg nickel-63 per kg body weight, 78% of the radioactivity was excreted in the urine during the first 24 hours. The half life ($t_{1/2}$) of serum nickel was 8.2 hours for the period from one to 48 hours following injection. During the first 24 hours, 90 per cent of the serum nickel-63 was protein bound, with only 10 per cent ultrafiltrable. Column chromatography on Sephadex G-25 of the ultrafiltrable fraction revealed the presence of five distinct complexes, only three of which appeared in urine. The half life of nickel-63 in the serum for the period from four to seven days following injection was found to be 95 days.(67)

Nickel and cobalt distribution were studied in the mouse zygote and early blastomeres. Nickel and cobalt were redistributed in the cytoplasm of the blastomeres during the formation of the blastocyst. After the eighth blastomere stage, granules that retained the nickel almost disappeared.(68)

3. Plants

In many green plants, degree of absorption of nickel by the roots appears to be dependent upon the soil pH. Raising the pH of serpentine or high nickel soils by the addition of lime usually somewhat alleviates the toxic effects of nickel.(69) The excessive absorption of nickel is thought to reduce the cation exchange capacity of roots in such diverse plants as oats, beans, peas, sunflowers and tomatoes.(70) Some plants indigenous to serpentine soils accumulate nickel less readily than nonserpentine species. Other plants accumulate nickel in large amounts. A study on the effects of ammonium and nitrate fertilizers on the uptake of nickel by some crop plants (wheat, barley, cotton, peanut, rye grass, rice, sorghum) and weeds revealed that more nickel is taken up from sandy or low nickel soils when the plants are fertilized, ammonium stimulating more uptake than nitrate. The concentration of nickel in the roots was greater than in the shoots of all plants with all treatments.(71)

B. Nutrition and Growth

1. Nonhuman Mammals

The growth of male dairy claves was retarded by dietary nickel levels of 250 or 1000 ppm as nickel carbonate.(72) The feeding by gelatin capsule of 500 mg of nickel as nickel chloride or nickel carbonate to calves resulted in a decrease in voluntary intake of the regular diet. In a cafeteria feeding experiment, the palatability of regular feed to the calves was decreased by the addition of 100 ppm nickel as nickel chloride or 500 ppm nickel as nickel carbonate to the feed. A linear depression of feed palatability as nickel concentration in the feed was observed. Nickel as the chloride had five times as much effect as nickel as the carbonate.(73)

When 700 mice were given drinking water containing 5 ppm nickel together with a cadmium-deficient diet, an increase in the mortality of males, but not females, was observed. No carcinogenic effects were detected, and the tumor incidence in females actually decreased. A moderate increase in nickel contents of organs occurred.(74) The addition of nickel to mouse embryo cell cultures resulted in a decrease in mitotic index and an increase in the number of abnormal mitotic figures observed. Nickel treated cultures showed increased retention of a histochemical stain specific for protein-bound sulfhydryl groups during telophase and post-telophase stages.(75)

2. Nonmammalian Vertebrates

The growth of chicks up to four weeks of age was significantly depressed by dietary nickel levels of 700 ppm and above.(76)

3. Plants

Cotton development and yield was positively influenced by the addition of nickel and zinc to the soil due to enhancement of the exchange of nitrogenous substances in the plant.(77) The green alga, Chlorella vulgaris, shows optimum growth on a purified medium containing three micrograms nickel per liter.(78)

4. Microorganisms

After six hours growth in a medium containing 4×10^{-4}M nickel chloride the marine bacterium, Arthrobacter marinus, was greatly enlarged from its normal 2 by 4 micron size to 10 to 15 microns in diameter. Electron micrographs revealed a greatly plasmolyzed megalomorph, in which the inner dense layer of the cell wall had disappeared, leaving a light-dense profile. The cytoplasmic membrane and the nuclear material did not appear changed.(79) No cell division occurred when nickel chloride concentration was 5×10^{-4}M, and the lag phase of the culture was increased from the normal three hours without nickel to more than 70 hours with 4×10^{-4}M nickel chloride. As nickel concentration increased, the maximum cell population decreased.(80)

C. Electrophysiology

1. Nonhuman Mammals

In mammalian muscle preparations, nickel (II) can abolish contractions, but not excitation. Increasing the calcium (II) concentration can overcome the inhibition of contraction. The application of 2mM nickel (II) via Tyrode electrode to pig papillary muscle in the presence of 1.8 mM calcium (II) produced the above inhibition effect. When applied to the surface of the muscle, nickel (II) could replace calcium (II), and the action potential retained its normal shape.(81) In the rabbit pulmonary artery preparation however, nickel (II) could not substitute for calcium (II) in the normal contractile response to applied noradrenalin or sympathetic nerve stimulation.(82) In isolated cat trabeculae (myocardial fibers), 2mM nickel (II) prevented contraction by reducing calcium (II) conductance of the membrane, but sodium conductance was not affected. Increasing the calcium (II) concentration overcame the effect of the nickel.(83) The addition of nickel (II) to a preparation of kitten atrial fibers produced a rapid and exponential decay of contractile force generated, but no apparent effect on ventricular electrical activity. The calcium (II) dose-response curve was shifted to the right without a reduction in maximum tension, so that increasing the calcium (II) could produce in the original contractile force. That no calcium (II) could be detected in the effluent of the perfusate shows that calcium (II) was not displaced by nickel (II). Gas perfusion of the preparation after nickel (II) had reduced the contractile force to one gram resulted in a gradual increase to 60% of the control value.(84)

2. Nonmammalian Vertebrates

Studies on amphibian nerve and muscle preparations reveal that the major effect of nickel (II) is the prolongation of the action potential. Nickel (II) increases membrane permeability to sodium and potassium ions, resulting in less of a concentration gradient and a higher resting potential.(85) Increasing the nickel (II) concentration applied to a frog ventricular strip from 0.42 to 20 mM produced the development of a focus of spontaneous activity, an artificially created rhythm initiator similar to the natural sinus venosus rhythm initiator.(86) Nickel (II) increased the duration of the action potential by activating the Mn - inhibitable sodium-calcium channel.(60) The action potential amplitude was not affected.(87) When calcium (II) was replaced by nickel (II) in a frog toe muscle preparation, the threshold of contraction stimulated by potassium ions was raised. The size of contractions was also increased.(88)

The application of nickel (II) to the nodes of Ranvier of isolated frog nerve fibers produced a prolonged action potential with an increased amplitude, but less steep ascending slope.(89) The time required for repolarization was longer, resulting in longer duration of the refractory period to another action potential.(90) The maximum decrease in membrane impedance coincided with the action potential peak, and impedance did not return to the resting level until 7 to 43 msec after the end of the action current.(91)

D. Metabolic Effects

1. Human

Nickel inhibits human breast 5-nucleotidase, but not alkaline phosphatase.(92,93) Lymphocytes from 7 out of 12 nickel hypersensitive patients were observed to take up carbon-14-thymidine when the culture was incubated with nickel at a concentration of 10^{-4} meq per ml. No control lymphocytes were so stimulated by the presence of nickel ions.(94)

2. Mammals

The metabolic fate of nickel carbonyl has been studied with $Ni(^{14}CO)_4$ and $^{63}Ni(CO)_4$ in rats injected intravenously with an LD_{50} dose. Thirty-six per cent was exhaled unchanged within six hours after injection. Intracellular degradation of most of the remainder to nickel (II) and carbon monoxide took place, and carbon monoxide reached maximum hemoglobin saturation levels two hours following injection. Only 1.1% of the injected $Ni(^{14}CO)_4$ was exhaled as $^{14}CO_2$, and less than 1% was excreted in the urine after 24 hours.(95)

Injection of rats with an LD_{50} dose of nickel carbonyl (2.2 mg Ni/100 gm body weight) drastically reduced liver RNA synthesis 24 hours after injection as measured by carbon-14-orotic acid incorporation into liver RNA. Without nickel carbonyl treatment, the mean specific liver RNA activity in rats killed 40 minutes after an injection of ^{14}C-orotic acid was 318 ± 133 µmoles ^{14}C per mole ribose.(96) The rate of RNA synthesis by a chromatin-RNA polymerase complex was decreased six hours after LD_{50} injection of rats from 0.3 ± 0.03 to 0.16 ± 0.02 µmoles tritiated-cytidine triphosphate per gm DNA.

The molar ratio of nickel to DNA nucleotides in the chromatin-RNA polymerase averaged 0.046, the concentration of nickel in the final assay mixture equalling 3.4×10^{-6}M. The *in vitro* addition of 1×10^{-5} parts of nickel carbonyl or nickel chloride to chromatin-RNA polymerase complex from controls did not inhibit incorporation of ^{3}H-cytidine triphosphate. The site of *in vivo* inhibition is unclear since the fact that an intact nuclear membrane is unnecessary for the inhibitory action of nickel carbonyl indicates that it does not exert its effect by impairing transmembrane transport of RNA nucleotides.(97) Nickel carbonyl does not decrease lung RNA synthesis as it does in liver.(98)

Perhaps the effect of nickel carbonyl on RNA synthesis in the liver can at least partially account for the way in which it reduces the activity of several liver detoxification enzymes. Rats exposed to nickel carbonyl by inhalation (0.2 mg Ni per liter of air) or injection (2 mg Ni per 100 gm body weight) had diminished benzpyrene hydroxylase activity in liver and lung. In lung the enzyme activity in treated rats 52 hours after exposure was 1.1 ± 1.0 units compared with the control, 9.5 ± 4.3 units, in liver, the activity dropped to 113 ± 24 units compared with 295 ± 123 units. The minimum activity occurred two to three days after exposure and returned to normal after a week. Nickel carbonyl did not inhibit benzpyrene hydroxylase *in vitro*.(30) The same dose of nickel carbonyl reduced the activity of hepatic tryptophan pyrrolase from 36 ± 7 units in rats treated with cortisone and nickel carbonyl. Nickel carbonyl did not inhibit tryptophan pyrrolase *in vitro*.(30) An LD_{50} dose of nickel carbonyl had a similar effect on aminopyrine demethylase in rats.(99) Nickel carbonyl may exert its carcinogenic effects by repressing these detoxifying enzymes, prolonging the tissue retention times of the carcinogenic substrates for the enzymes.

Other liver effects have been observed in rats after exposure to nickel carbonyl. Elevation of hepatic ATP by 12% occurred 30 minutes after an LD_{50} injection of nickel carbonyl to rats, and ATP of injected rats was still 13% above control levels 24 hours after injection.(100) Twenty-four hours after exposure to nickel carbonyl by inhalation (80 ppm for 30 minutes), the 3 molar sodium chloride precipitable fraction of both liver and lung RNA was elevated 196% and 50% respectively. This RNA fraction accounts for 50% respectively. This RNA fraction accounts for 34% of the lung RNA and 23% of the liver RNA in controls.(101)

In rat adipose tissue (from the epididymal fat pad), nickel (II) enhanced carbon-14-glucose uptake, oxidation of ^{14}C-glucose to $^{14}CO_2$ and incorporation of labelled glucose into fat pad lipids, as well as glycogen.(102) Nickel (II)-aminoacid complexes affected serum lipids in rabbits by increasing total serum lipids, and in particular free fattyacids and cholesterol.(103)

Guinea pig uteri were stimulated by treatment with 0.01 - 3.0 mM nickel (II). The alkaline phosphatase activity and localization of some nickel-stimulated uteri differed from the normal histamine-stimulated uteri. Especially strong alkaline phosphatase activity was observed in the cell membranes of the endometrium.(104)

In isolated spleens treated with phenoxybenzamine and ^{3}H-norepinephrine, ^{3}H-norepinephrine released by nerve stimulation was markedly reduced by perfusion with 1, 2.5 and 5mM Ni^{++}.(105)

Inhibition of beef liver glutamic dehydrogenase by metal binding agents such as 1, 10-phenanthroline could be prevented by the addition of nickel (II), as well as zinc (II), copper (II), cadmium (II), iron (II), cobalt (II), manganese (II), but not magnesium (II).(106) Nickel (II) restores activity to metal-free allantoicase, and protects the enzyme against heat denaturation at 30°C and above.(107) Purified horse liver arginase was also thermally stabilized by Ni^{++},(108) but feeding experiments with rats showed no activation of liver arginase by nickel (II) *in vivo*.(109)

In mouse L929 cell cultures grown on Eagle's minimum essential medium, interferon synthesis induced by Newcastle Disease virus was considerably inhibited by the presence of nickel chloride (0.18 mg/7 ml) in the medium. The inhibition persisted for several days, but was not permanent.(110)

3. Plants

Nickel (II) ions apparently inhibit degradative changes in plants associated with senescence and injury. In detached rice (Oryza sativa) leaves, treatment with nickel (II) retarded the breakdown of chlorophyll, protein and RNA.(111) Treatment of petunias with nickel sulfate suppressed the destruction of anthocyanin pigments in the flowers, preserving the color.(112) The effects of nickel (II) on respiratory chain enzymes in different-colored petunias was studied by incubating half-opened buds for two days in 2mM $NiSO_4$. Nickel (II) considerably reduced the activities of specific dehydrogenases in all colors, except that pyruvate and α-ketoglutarate dehydrogenases were activated by nickel (II) in white flowers, and not affected by nickel (II) in colored flowers except in lilac flowers, which had slightly reduced activity for these enzymes. The activities of ascorbate oxidase and polyphenol oxidase were increased by nickel (II), but cytochrome oxidase was considerably inhibited.(113)

Nickel (II) inhibited chlorophyll formation in detached leaves of khapli wheat.(114)

The effects of nickel on two species (Vicia faba L. and Helianthus annuus L.) grown hydroponically with complete nutrients indicated that surplus nickel may cause changes in the structural characteristics and chemical organization of biopolymers. High nickel concentrations produced decreased mitotic activity in V. faba and structural changes in the cell chromatin in H. annuus.(115)

4. Microorganisms

In yeast cells, nickel (II) can exert an inhibitory effect on fermentation in at least two ways: inhibition of alcohol dehydrogenase(116) and inhibition of active transport of metabolizable sugars into the yeast cells.(117) The uptake of metal ions into a nonexchangeable compartment by yeast cells was small in starved cells, but stimulated 5 to 20 fold by glucose and phosphate pretreatment. The metal ion uptake, in which two potassium ions (or two sodium ions) were exchanged for each divalent metal cation, occurred under aerobic or anaerobic conditions. Reduced uptake occurred at low pH's less than 5.0. Nickel (II) inhibition of fermentation was alleviated at low pH's implicating a transport effect, but flushing the cultures with gas, the presence of alcohol and acetaldehyde, or increased glucose or oxygen concentration can also affect sugar transport and enzyme activities.(116) Nickel appears to inhibit the first step in sugar transport by interactions with the polyphosphates involved. Increasing the temperature increased the inhibition. However, in iodoacetate-treated cells, the carrier-mediated facilitated diffusion of sorbose and glucose was not affected by nickel (II).(117)

In *Bacillus subtilis*, nickel (II) was found to be able to replace magnesium (II) for citrate transport.(118)

The narcotic effects of nickel (II) on ciliated protozoans were demonstrated to be related to precise enzymatic reactions in studies with *Paramecium caudatum*, *P. aurelia*, *Colpidium*, *Tetrahymena rostrata* and *Euplotes patella*. Resistance to nickel (II)-induced anesthesia varied with pH, nickel (II) concentration, and subclone type, and was enhanced by the presence of certain metabolic inhibitors which reduced the available ATP. Apparently, resistance to nickel (II) narcosis is determined by the membrane permeability to nickel.(119, 120)

Evidence for the active transport of nickel (II) by *Paramecium caudatum* is as follows:(119)

(1) ionic movements occur against the concentration gradient;

(2) the intracellular nickel concentration is inexplicably by passive diffusion;

(3) the kinetics of penetration follow Michaelis laws;

(4) only a limited number of penetration sites exist; and

(5) ATP is required.

Strontium ions antagonize nickel (II) anesthesia in *Paramecium* and reduce the inhibitory effects of nickel (II) on fission.(121)

The RNA-dependent DNA polymerase of Rous sarcoma virus was inhibited by nickel (II), however, nickel (II) had little effect on the transforming ability of the virus(122) (perhaps related to nickel (II) inhibition of interferon synthesis).

E. Cytotoxicity

The effects of nickel (II) on laved rabbit alveolar macrophages were examined *in vitro*. The cell viability was reduced by 50% after 20 hours with 4.17 millimolar nickel (II) chloride. Cell number was not decreased until the nickel concentration was 12.8 millimolar. Nickel (II) inhibited acid phosphatase activity by 50% at a concentration of 3.80 millimolar.(123)

Cultured human lung fibroblasts were more sensitive to nickel (II) than rabbit alveolar macrophages. The LC_{50} was 2.83 millimolar nickel (II) chloride. Uptake of precursors of nucleic acid and protein synthesis was 50% inhibited by much lower nickel concentrations. Nickel (II) considerably reduced phagocytic activity of rabbit alveolar macrophages, and the effect was concentration dependent. For example, with 1.11 millimolar nickel (II) chloride, cell viability was still more than 80% of control values, but the phagocytic index, a measure of the ability of trypsinized macrophages to ingest polystyrene-latex spheres 1 micron in diameter, was less than 20% of control.(124)

F. Therapeutic Uses

1. Humans

The nickel (II) chelate of 3, 4, 7, 8-tetramethyl-1, 10-phenanthrolene (Niphen) proved to be as effective as hexachlorophene in the prophylaxis of staphylococcal injections in the newborn and patients undergoing elective obstetric or gynecological surgery. Niphen also provided rapid relief of symptoms of chronic monilial and trichomonal vaginitis. Successful control of secondary infections in adolescents with longstanding acne vulgaris was also achieved with Niphen. No toxic manifestations were observed in any clinical trials.(125)

2. Invertebrates

Silkworm losses from "spontaneous" jaundice were decreased by 3.8 times after spraying the mulberry leaves with 0.05% nickel sulfate. This treatment increased cocoon formation by 18 per cent.(126)

3. Plants

The effectiveness of nickel (II) salts in the treatment of fungal infections of grains has been demonstrated repeatedly. Treatment of Thatcher with the leaf rust, Puccinia recondita, stopped the respiration and growth of the fungus.(127) Protective fungicidal activity against the leaf rust, Puccinia rubigo-vera f. sp. tritici, and stem rust, Puccinia graminis var. tritici, of wheat was achieved by application of the acetate, sulfate, nitrate and chloride salts of nickel (II) at a nickel concentration of 70 ppm. The nickel salt amine complex RH-1, (bis [N-(2 hydroxyethyl) dodecylbenzylamine] nickel (II) chloride), was effective at 280 ppm nickel. The order of effectiveness as eradicative fungicides was: RH-1 = nitrate = chloride>sulfate = fluoride = acetate. The nickel concentration necessary for the eradication of stem rust was twice that needed for leaf rust. Eradication of the crown rust of oats (Puccinia coronata avenae) and sunflower rust (Puccinia helianthi) required nickel concentrations very close to phytotoxic levels. Simulated rain removed the protective action of the inorganic nickel salts more easily than that of the RH-1.(128) A field study showed that two or three applications of nickel chloride or nitrate hexahydrate at seven or eight day intervals at one pound per acre in fifty gallons of water gave reasonable control of leaf rust and stem rust on Thatcher, Marguis and Red Bobs Wheat even if spraying was delayed until the rust was present.(128,129)

RH-1 was the most effective nickel (II) salt amine complex among four which exhibited eradicative and protective action against leaf rust of wheat (P. rubigo-vera) in a field study.(130) Wheat stem rust (P. graminis tritici Erkiss) infections were reduced after treatment with $NiSO_4$, $NiCl_2$ and $Ni(NO_3)_2$, but $Ni(NH_4)_2(SO_4)_2$ was ineffective.(131) The application of well-timed sprays containing nickel salts and dithiocarbamate to Marquis wheat (Triticum aestivum L.) delayed leaf rust (P. graminis f. sp. tritici) development for 18 days and stem rust (P. recondita) development for 12 days, resulting in 66% control of rust.(132) The addition of nickel salts to the organic fungicides maneb or zineb clearly improved the control of crown rust (P. coronata Cda. var. avenae Fraser and Led.) of oats (Avena sativa) over the use of maneb or zineb alone.(133) Rye leaf rust (P. rubigo-vera f.) was eradicated by topical applications of nickel salts during the "Fleck stage". The protective, but not the eradicative, ability of the nickel salts was destroyed by artifical rain.(134) Nickel salts are also useful in the control of the mint rust fungus, P. menthae.(135)

The blister blight fungus (Exobasidium vexans Massee) on tea leaves may be controlled by $NiCl_2$.(136) Sporulation of E. vexans on tea leaves was suppressed by the applications of nickel chloride, nickel sulfate, nickel nitrate or nickel acetate at nonphytotoxic concentrations of one or two grams per liter in the lab and field. (Three grams per liter was slightly phytotoxic). Blister development was inhibited 16% and 55% by $NiCl_2$ applied at strengths of 0.4 and 1 grams per liter, respectively. Two grams of $NiCl_2$ per liter prevented lesion formation even 48 hours after application.(137)

Asparagus rust (P. asparagi) lesions were decreased by treatment of asparagus with a mixture of maneb and nickel sulfate.(138)

IX. ENVIRONMENTAL EFFECTS

A. Persistence and Degradation

The distribution of metals in the solids of waters of two streams in Tennesee was studied. The dissolved solids had the lowest concentration of metals, but contained 90 per cent of the total metal. The colloidal particle fraction, consisting of particles from 100 to 1500 Å, had the highest metal concentration, but contained less than one per cent of the total. The coarse particulates, greater than 1500 Å in diameter, contained less than ten per cent of the total metal.(140)

B. Environmental Transport and Contamination

1. Endogenous

Some soils and waters in the world contain significant amounts of nickel. For example, endogenously high levels of nickel and some other metals occur in the serpentine soils of Scotland, New Zealand, Southern Rhodesia and Portugal.(141,142) The nickel content of mineral waters in Germany may vary from 0.1 to 370 micrograms per kilogram. The Co:Ni ratio ranges from 1:3 to 1:6.(143)

2. From Use

Environmental exposures of humans to large amounts of nickel may occur through foods and other commodities. Wine and beer quality is reduced by the presence of nickel in trace amounts.(144,145) The effect can be eliminated by the addition of EDTA.

Some commercial detergents in the Netherlands contain 2 to 9 ppm nickel (0.2 - 0.8 micromolar), almost a sufficient enough level to induce allergic reactions in nickel sensitive persons. The addition of EDTA to detergents yielded no discernible decrease in nickel contact allergic reactions.(146)

Investigations on the heavy metal content of tobacco smoke have led to conflicting conclusions. In one study of the analysis of smoke from eight different types of cigarettes, the workers concluded that it was doubtful that amounts of nickel inhaled reach cancerigenic levels.(147) Another study revealed that 20 per cent of the total nickel content in cigarettes (1.59 to 3.07 micrograms of nickel per cigarette) was present in the mainstream of smoke inhaled. At this rate, the amount of nickel in the smoke inhaled by a heavy smoker in one year is equal to three times the amount necessary to induce pulmonary cancer in the rat.(148) In a third study using cigarettes containing 4.25 to 7.55 micrograms nickel per cigarette, 0.4 to 2.4 per cent of the nickel in the smoked portion of the cigarette was present in the particulate fraction of the mainstream smoke. Eleven to thirty-three per cent of the nickel was found in the sidestream smoke, indicating a possible hazard to non-smokers.(149)

Concentrations of nickel in roadside soil and grasses, and variation with increasing distance from the road and increasing soil depth have been studied.(150)

3. Industrial

Environmental increases in nickel content due to man's activities have been reported in several areas of the world. Nickel analysis of plant samples (Hypnum cupressiforme) collected from two regions of Sweden from 1870 to 1943 revealed that a large rise in nickel content occurred around 1920, when nickel was introduced into world production. The nickel content of the plant samples collected in 1968-1969 was twice the 1920 levels. Samples collected from Skane in southern Sweden contained significantly greater amounts of nickel than those from Gotaland, in the northeast. This rise in nickel is attributed to the increase in airborne nickel due to human activities. Skane samples contained more nickel because they were located closer to the industrial sources in Central Europe.(151)

Studies on the hydrochemistry and hydrobiology of the Wislok River in the Krosno Region of Russia, an area polluted with heavy metals and cyanide, revealed that high concentrations of metals sterilized the river, but even lower concentrations unfavorably affected the communities involved in self purification.(152)

The soil in the heavily industrialized Sudbury Basin in Ontario contains high levels of metals due to airborne contamination.(153) The lichens in the area have a high content of heavy metals. Since metals are less toxic to lichens and other epiphytes, these organisms are potentially the most useful indicators of heavy metal fallout around industrial areas.(154) The tap water of Sudbury, Ontario contains almost 200 times the nickel concentration of the water of Hartford, Connecticut, which is 1.1 ± 0.3 micrograms nickel per liter.(155)

A nickel concentration of 122 ppm was found in soil solutions from acidic coal mine spoils material. More nickel was extracted in solutions of higher pH.(156) It appeared that even after adjustment of soil pH for otherwise satisfactory plant growth, nickel was likely to remain in solution in toxic amounts.(156)

The introduction of nickel, zinc and copper into Lake Michigan by atmoshperic fallout evidently exceeds the input from unpolluted streams emptying into the lake.(157)

C. Bioaccumulation and Content

1. Humans

Serum and urinary nickel in healthy persons in two cities reflected nickel levels in tap water in kind, but not in degree:

Nickel Concentration (mg/l)(155)

Site	Tap Water	Serum	Urine
Sudbury, Ont.	200 ± 43	4.6 ± 1.4	7.9 ± 3.7
Hartford, Ct.	1.1 ± 0.3	2.6 ± 1.0	2.5 ± 1.4

2. Mammals

Nickel elevation in the tooth enamel of rats fed a cariogenic diet containing nickel acetate was observed. Caries inhibition in females, but not males, was obtained on this diet, but no definite correlation between caries and level of nickel in enamel could be ascertained.(158)

3. Nonmammalian Vertebrates

Nickel was clearly detected in bodies of fish killed by nickel sulfate and nickel plating solutions, and also in fish living in such solutions. Nickel was not detected in the bodies of normal fish.(159)

4. Invertebrates

Nickel was determined in the skeletons and forage plants of two species of sea urchins, but no direct correlation was observed. Echinometra lucunter L. contained more nickel than Tripneustes esculentus, but the principal forage plant, Padina gymnosperma, of the latter, had higher nickel levels than Thalassia testudinum, the principal forage plant of the former.(160)

5. Plants

Nickel analysis of the foliage ash of six species of plants grown on serpentine soil in New Zealand revealed species differences in ability to accumulate nickel. Pimelea suteri, a serpentine endemic, showed the highest nickel concentrations. No universal mechanism of tolerance or exclusion however, could be applied to explain differences.(161) Nickel contents of plants grown on serpentine soils, limestone and dolomite were studied in Bosnia. All plants grown on serpentine soils had higher metal contents than plants grown on limestone. The highest levels were found in some plants grown on any soil: Teucrium montanum, Potentilla tommasiniana and Sedum achroleucum. Definite serpentine plants, such as Halacsya sendtneri, Scrophularia tristis and Silene willdenowii var serpentina, often had lower nickel levels than many species grown on any soil. Plants grown on dolomite were rich in nickel, poor in iron, and sickly in appearance.(162) In the shallow serpentine soils of northeast Portugal, nickel toxicity is more or less intense, and the predominance of Alyssum serpylifolium ssp. lusitaniucm, a nickel accumulator, was noted.(142)

The intense infertility of serpentine soils of southern Rhodesia is related to the high nickel and chromium content (maximum 4000 ppm). The amount of exchangeable (HCl soluble) soil nickel closely correlated with nickel content of indigenous grasses. On a soil with 70 ppm exchangeable nickel, oats exhibited transverse-banded leaves due to white chlorosis, and lucerne exhibited intense yellow chlorosis within two days of emergence, and died within forty. The addition of $CaCO_3$ to the soil increased soil pH from 5.9 to 8.2, and reduced the nickel content of dried oat leaves and stems from 233 to 84 ppm. The toxic effects were reduced, but not eliminated.(141) Plants growing on mining and smelting heaps in Silesia, which contain high nickel, as well as iron, calcium, and magnesium, but decreased organic compounds and water, exhibit wide diversity in kind, degree, coverage, and level of succession. Of 45 species examined, Cerastium arvenae, Plantage lanceolata, Tussilago farfara, and Campanula rotundifolia (in dwarfed form) accumulated nickel. The ash of these four species contained ten times the nickel normally found, perhaps explaining the dwarfing of C. rotundifolia.(163) A small shrub in western Australia may represent the highest relative accumulation of nickel on record. Hybanthus floribundus contains up to 23 per cent nickel by weight in its leaf ash.(164)

The nickel and cobalt content of plants used in Swazi snuff was closely related to the soil content of these metals.(165) The seeds of leguminous plants have a higher nickel content than the seeds of grasses grown in the same area.(166) The amount of nickel in honey and pollen from the Maritime Regions of the Ukraine varies widely in relation to geographical zone. A range of 0.28 to 0.84 mg nickel per kg was found in honey ashes, and from 0.14 to 1.29 mg nickel per kg pollen ash.(167) The average nickel content of 44 varieties of spinach from all over the world was 0.42 mg nickel per 100 gm dry leaves.(168)

X. TOXICITY

A. Humans

1. Chronic Toxicity

Four hundred fifty-eight workers in the nickel electrolytic refining industry in eastern Europe were examined by x-ray. Inflammatory processes of subatrophic and atrophic character were associated with the chronic inflammation of accessory sinus cavities in 33.07% of the workers. These processes were apparent in 17.75% of workers suffering from acute sinusitis and in 22.05% with cysts and cyst-like formations.(169) High incidence of various blood irregularities were noted in eastern European workers producing nickel ferrite powders. Twenty-five percent developed thrombocytopenia, anemia and leukopenia, 35% exhibited eosinophilia, 14% had monocytosis and 50 per cent had decreased osmotic erythrocyte resistance.(170) Occupational diseases of workers in the electrolytic refining of nickel are apparently caused by the inhalation of an atmosphere of aerosol solutions of nickel chlorides and sulfates. The microclimate of such plants is also characterized by heat and moisture. Pure nickel production via the carbonyl cycle is related to the danger of contamination of the air by nickel carbonyl.(171) Nickel carbonyl poisoning by inhalation in 46 workers in a soda and aniline factory in Ludwigshafen, Germany, on the Rhine during the period 1952-1967 consisted of 39 light poisonings, 7 severe cases and 2 deaths. The clinical symptoms were headache, dizziness, chest pain, nausea, fever, coughing, and bronchial pneumonia; pulmonary edema occurred from one to forty-eight hours after exposure. The urine nickel concentration was a good index of degree of poisoning: greater than 10 micrograms per deciliter indicated poisoning and greater than 50 micrograms per deciliter indicated that hospitalization was required.

2. Acute Toxicity

The symptoms of acute $Ni(CO)_4$ toxicity in humans include the abnormally high position of the diaphragm, limited or absent respiratory motions, a significant decrease in pneumatization of pulmonary areas, intensification and lubricability of pulmonary patterns, the bilateral focality of various degrees of manifestation and a high position of the cardiovascular bundle.(172) In several young people pulmonary changes following $Ni(CO)_4$ intoxication were observed via x-ray. In two patients, intensification of the overall lung picture, as well as the roots of the lungs, was observed. Bilateral foci of exposure were observed in all. Retrograde development of changes in the x-ray patterns began 7 to 12 days after initial exposure. The principal $Ni(CO)_4$ effect appears to be the disturbance of lung capilllaries and arterioles.(172) Nickel carbonyl intoxication apparently does not leave any after-effects in healthy people.(172) Treatment of more than 300 workmen with acute nickel carbonyl poisoning with the chelating agent, diethyldithiocarbonate (Dithiocarb), prevented death in 100% of the cases.(100) In one severe case of total nickel carbonyl poisoning, diethyldithiocarbamate sodium did not prevent death, probably due to severe pulmonary and cerebral edema.(173) Dithiocarb has been shown to be effective in the mobilization of copper and nickel in patients with hepatolenticular degeneration (Wilson's disease).(174)

3. Allergies and Sensitization

Nickel dermatitis can be induced in humans through contact with nickel-plated articles,(175,176) industrial exposures to nickelous dusts or baths, or internal exposure to nickel.(177) The symptoms comprise two levels: 1) a simple dermatitis at the area of contact, the typical "nickel itch", consisting of burning and itching of the exposed skin; and 2) a chronic eczematous reaction, in which erythema occurs, and later nodules, which may eventually form pustules, appear in the web of the fingers and the forearm.(178)

Symptoms may be relieved within a week by removal from exposure, but a rash may persist for some weeks. Specific desensitization to allergic dermatosis induced by nickel, chromium or cobalt, can be achieved by increasing doses of the specific allergen or one of the other two metals.(179) The duration of the rash after avoidance of contact with an allergen is highly variable, but it seems to last longer in cases of nickel sensitivity than in other types.(180)

Nickel sensitivity is usually determined by patch testing with a 5% $NiSO_4$ solution. Out of 200 patients tested in one study, 13.5% exhibited positive tests, 85.2% of whom had a previous history of nickel contact dermatitis.(181) In a study of 5416 persons tested for nickel, chromium or cobalt allergy, 9.9 % showed a positive reaction. Seventy-seven per cent of the allergic women were sensitive to nickel; 87% of the allergic men were sensitive to chromium. This difference in sensitivity is presumably due to differences in exposures to sensitizing contacts.(182) In another study on 1000 patients, 64% of sensitive women were suspected of nickel allergy.(183)

Nickel sensitivity and atopy are apparently unrelated. Only 11% of the persons with a personal or family history of proven nickel dermatitis exhibited atopy.(184)

A study of 25 workers engaged in electroplating with nickel, chromium, copper, and zinc revealed seven who suffered dermatosis. The dermatosis disappeared when workers took their annual vacation but recurred when they returned to work. The proportion of nickel dermatosis was much greater when the bath temperature was 60°C than when the temperature was 35 to 40°C.(185)

Apparent cross-sensitization between nickel and chromium or cobalt seems to be due to the presence of several allergenic metals in the sensitizing contact rather than to true cross-sensitization. In a study of nickel platers in Finland from 1949-1964, only 16% of nickel-sensitive workers also showed cobalt sensitivity; in all but two of these cases, the cross sensitization occurred during a period when cobalt was added to the nickel plating bath as a brightener.(186) Sixty three per cent of 87 patients with suspender eczema exhibited cross-sensitivity. Suspenders contain both metals.(186) More people with cement eczema were sensitive to cobalt than to nickel, but cement also contains both elements.(187)

The nickel sensitivity threshold in eczematous patients with nickel allergy was investigated by patch testing. The mean threshold (n=53) was 0.43% when distilled water was the solvent, and 0.51% when the solvent was petrolatum. Patients with combined nickel-cobalt sensitivity had the lowest thresholds (below 0.039%). No correlation was observed between degree of sensitivity and severity of skin disease.(146)

The eliciting safety limit, or the concentration of nickel which does not elicit any contact allergic reaction in highly sensitized persons, is one **micromole** of nickel per liter. This is also assumed to be the sensitizing safety limit of nickel.(188)

Evidence of cellular hypersensitivity in cultured lymphocytes and leucocytes, but not skin explants,(189) from nickel-sensitive patients as compared with normals has been reported. When treated with nickel sulfate or nickelacetate (10^{-4}meq Ni^{++}/ml), cultured lymphocytes from nickel-sensitive patients exhibited an increased percentage of conversion to lymphoblasts, accompanied by an increase in ^{14}C-thymidine uptake, indicating DNA synthesis. Macrophage migration inhibition was also observed.(94,190) However, no differences were observed in the effects of different nickel concentrations on mitotic capacity of leucocytes from nickel-sensitive and normal patients,(191)

4. Carcinogenicity

The blastomogenic properties of nickel compounds in humans and in rats have been well established.(192) Various environmental exposures to nickel seem to correlate with increased incidence of tumors in man. For example, cancer in the maxillary antrum of snuff users may result from using plant material grown on soil high in nickel. In Bantus, carcinoma of the maxillary antrum accounts for 45.5% of all respiratory cancers observed. The Swazi snuff used by these people contains high concentrations of nickel, chromium, and zinc.(193) The incidence of lung cancer was studied in 845 men employed by a nickel refinery in South Wales for at least five years beginning during or before April, 1944. In men first employed before 1925, the incidence of death due to lung cancer was 5 to 10 times the national average, and to nasal cancer, 100 to 900 times the expected mortality. After 1925, death rates due to lung and nasal cancer were comparable to those of other men in the same geographical region. Susceptibility to nasal cancer varied with age at first exposure, but susceptibility to lung cancer varied irregularly.(194) In a study of the high mortality of nickel concentration and smelting workers due to various cancers and sarcomas compared with the general population, the highest incidence of pulmonary carcinoma was observed among forty-year-old males. The incidence was higher for workers in roasting, reduction and cobalt departments who were exposed to nickel sulfides and oxides, as well as cobalt and and arsenic compounds. Femoral and lung sarcomas were most prevalent among these workers, the males alone being affected.(195)

A recent increase in the incidence of cancer of the nose and accessory sinuses in workers in the industry producing pure nickel by electrolysis warranted a reevaluation of maximum allowable exposures, according to Tatarskaya.(195)

B. Mammals

1. Toxicity

a. Topical Application

Nickel sulfate applied as compresses to skin lesions in rabbits caused lethal intoxication.(196)

b. Inhalation

A single intratracheal administration of 50 mg of nickel production plant dust to rats resulted in hyperplasia of the lymphoid apparatus in all animals. The nickel content of the dust varied with the source, and additional effects were observed as shown in Table 13.(197)

Table 13

Composition and Effects of Nickel Production Plant Dusts

Source of Dust	Composition	Effects
agglomerate	2% Ni, 45.5% SiO_2, 25.9% iron oxides, 12.4% aluminum oxides	siderosilicosis
furnace	64.4% nickel oxides and sulfides	connective tissue nodes
electric furnace	95% nickel oxides	diffuse sclerosis of interalveolar walls

Rats were subjected to the inhalation of soluble and insoluble aerosols of nickel compounds. After two weeks exposure the inhalations of nickel oxides caused a significant increase in the number of alveolar macrophages (measured by a standard washing procedure): increased mucus production was observed in the rats after nickel chloride inhalation. Histopathological examinations of rats after exposure to either compound revealed morphalogical alterations and changes in cell sizes depending upon the length of exposure.(198)

The effects of the aspiration of finely dispersed particles (0.19 microgram) of metallic nickel at a concentration of 0.005-0.006 mg per liter were studied in dogs. After six months exposure, various physiological changes including disturbed hemopoiesis, changes in blood vessel wall permiability, and alterations in thyroid function were observed. Eleven to thirteen months after discontinuation of nickel exposures, the disturbed functions were partially restored, but local pneumosclerosis with gradual cardiopulmonary insufficiency developed.(199) Syrian golden hamsters were exposed to nickel oxide inhalation at a concentration of 10 to 190 micrograms per liter. After initial clearance, 20% of the nickel from the exposure remained in the lung, and 45% of this was still present 45 days later. However, no hamster died within the six month duration of the experiment.(200)

c. Oral Administration

In rats given daily peroral doses of 0.06, 0.12, or 0.3 mg $NiCl_2$ per kg of body weight for 13 weeks, weight increments were significantly less than that of controls, the lag being most pronounced in the 0.3 mg/kg group (only 10% that of control). The erythrocyte count was somewhat lower in nickel-treated animals after 60 days, and the blood catalase activity was lower than controls, also.(201) In male rats, severe lesions in germ cells and reduction of spermiogenesis developed after long term $NiSO_4$ intoxication. The selective noxious effect was on the testicular parenchyma, with very few observed changes in the liver and kidney.(202)

Twenty-three male dairy calves were fed 0, 62.5 250 or 1000 ppm nickel as $NiCO_3$ in their diet from 13-21 weeks of age. Feed intake and growth rate were slightly retarded in the 250 ppm group. Feed intake was greatly retarded with the 1000 ppm nickel, and the animals lost weight, appearing younger, but not emaciated. During the recovery period in which all groups were fed a 0 ppm nickel diet, the growth rate of all was normal. Digestibility coefficients were not affected by a dietary nickel, but nickel retention was significantly lower than control in the 1000 ppm nickel group, probably due to the decreased feed intake. Rumen propionate increased and butyrate decreased on a molar basis. Organ weights were unaffected by dietary nickel, but the kidneys became nephritic, the severity of nephritis increasing with higher dietary nickel levels.(72) Nickel chloride was much more toxic than nickel carbonate to young dairy calves fed 500 mg of nickel per day in gelatin capsules. Nickel as nickel chloride has five times as great an effect as nickel carbonate on reducing the palatability of feed presented to seven-month old dairy heifers in a cafeteria experiment.(73)

The incidence of lethal legume bloat in cattle was increased 10% in cattle fed alfalfa-containing nickel. Although incidence of bloat exhibited a positive correlation only with the alfalfa content of protein Fraction I, nickel was found to have an important relationship to the amount of bloat that can occur.(203)

d. Injection

Intravenous administration of $Ni(CO)_4$ to rats at the LD_{50} dosage of 2.2 mg per kg of body weight resulted in liver and lung effects. Electron micrographs of liver cells revealed diffuse dilatation of the rough endoplasmic reticulum and nucleolar aberrations two to twenty-four hours after injection, but mitochondria and other organelles appeared essentially unaffected.(204) The earliest effects of LD_{50} $Ni(CO)_4$ injection on pulmonary alveoli occurred six hours to two days after injection and were manifested by intense swelling of the alveolar endothelium. Proliferation and hypertrophy of the alveolar epithelial cells occurred two to eight days after injection (peak at four to six days), and focal infiltration of the alveolar interstitium with connective tissue cells was present on the fourth and fifth days after injection. Histochemical studies of lung tissue two to six days after injection revealed the clumping of nuclear chromatin, bizarre mitoses, increased nucleolar and cytoplasmic RNA and augmented protein staining. Ultra-structural changes were also observed.(204) The LD_{50} for $Ni(CO)_4$ varied with the route of injection:

Mode of injection	Rat LD_{50} (mg Ni/100g body wt.)
intravenous	2.2 ± 0.11
subcutaneous	2.1 ± 0.42
intraperitoneal	1.3 ± 0.14

The pulmonary parenchyma was observed to be the target organ regardless of the route of administration.(204)

In mice the LD_{50} for subcutaneous injection of disulfonickelguanidine was found to be 240 mg per kg body weight. Subcutaneous injection of dogs with 4 mg of disulfonickelguanidine resulted in a decrease in blood pressure of 10-15 mm Hg. Injection of 0.3 - 0.5mg/kg did not produce changes in coronary blood flow or volumes in cats. A 2-4 mg/kg injection caused a 40-45% increase in coronary blood flow 3 to 5 minutes after injection in the cats, which returned to normal in 10 to 15 minutes. A simultaneous 20-25 mm Hg drop in blood pressure and increase in the oxygen consumption of the myocardium were also observed.(205)

e. Implantation

The histopathological reaction of the brain to the presence of nickel-coated shotgun pellets was observed in cats. Copper-coated pellets stimulated a more severe reaction, and lead-coated a less severe reaction.(206)

Pure nickel implants in the precentral motor cortex of monkeys produced evidence of severe nickel toxicity and severe necrotizing foreign body reaction. Some epileptogenic effects were observed.(207)

2. Sensitization

Nickel allergic reactions may be induced in guinea pigs following surface and subcutaneous administration of nickel salts.(208) Dietary vitamin C supplements protected guinea pigs from nickel dermatitis induced by repeated applications of 1:50,000 nickel sulfate ointment to the skin, unless the nickel treatment was accompanied by local injections of Freund's adjuvenant or potassium alum.(209) In experimental Corynebacterium acnes injection, pustular patch tests were regularly produced by five per cent $NiSO_4$.(210)

An increase in nickel content of total serum protein, and especially in the β_1 and β_2 globulins, accompanied nickel sensitization in guinea pigs, but no complete parallelism between degree of allergic reaction and β globulin nickel content was observed.(211) The quantitative reaction kinetics of nickel binding to various proteins, including human serum, as studied by equilibrium dialysis and paper electrophoresis, showed that binding is primarily to carboxyl and amino terminals, making it unlikely that nickel itself behaves as a hapten, capable of initiating allergic response.(212) Starch gel electrophoresis of serum protein revealed that the effect of nickel ions on serum protein precipitation was much less than the effect of mercury, lead or copper divalent ions.(213)

Four or five "tumor-specific" antigens have been identified in nickel sulfide-induced rhabdomyosarcomas of rats. Serum from tumor-bearing and immunized rats contained tumor-specific antibodies. Cells from different tumors did not cross-react significantly, but cells from the same transplanted tumor cross-reacted through several successive generations. The antigens appeared to be located in the cytoplasm of the tumor cells.(214)

3. Carcinogenicity

In rats and guinea pigs, the long-continued inhalation of powdered nickel metal resulted in multicentric adenomatoid formations of alveoli and hyperplastic proliferations of terminal bronchiolar epithelium. Both malignant and benign pulmonary lesions were observed in guinea pigs.(215) However, pulverized fragments of nickel metal applied on a fibrous glass vehicle to the pleura of rats did not induce tumors within two years.(216) Nickel powder was used to induce fibrosarcomas in Fisher - 344 rats. The tumors could be transplanted to host rats of the same strain.(217) In primary rhabdomyosarcomas induced by the intramuscular implant of nickel in rats, the nickel concentration in the tumor was found to decrease from the center to the periphery and decrease with increasing age of tumor. Most of the nickel present was bound to the nuclear fraction, with smaller amounts in the mitochondrial and soluble fractions of the tumor cells. The tumors apparently did not need or concentrate nickel ions once induced.(218) In rats, the inhalation of an amount of $Ni(CO)_4$ comparable to that inhaled by a person smoking fifteen cigarettes a day for one year resulted in the appearance of various pulmonary cancers (squamous cell carcinoma, adenocarcinoma, anaplastic carcinoma) 24 to 27 months after exposure. The death rate in rats three years after exposure was three times that of controls.(33) Bethesda Black rats were found to be more resistant to tumors induced by intramuscular injection of nickel sulfide than Hooded rats. At the site of injection, in the Bethesda Blacks, large masses of phagocytic cells appeared and engulfed the nickel sulfide powder without undergoing obvious damage. The phagocyte aggregation persisted at the site at least fourteen months, in some cases becoming surrounded by lymphocytes. The phagocytic ingestion may result in subcarcinogenic levels of nickel remaining in the tissue. The lymphocytes may be involved in the immune response.(219) The form of the nickel sulfide intramuscular implant (free powder, powder within diffusion chamber, chips, discs) had no significant effect on the tumor incidence in rats, which was 71-95%. The average latent period for tumor development almost doubled when the carcinogen was contained within a diffusion chamber. The tumors produced were all locally-occurring rhabdomyosarcomas. It was observed that neither the walling-off of metal implants nor phagocytosis nor direct contact between the metal and the cells was necessary for tumorigenesis.(220) Induction of rhabdomyosarcomas in rats is not influenced by sex, castration or an increase in myotrophic steroid.(221) A cell line from nickel sulfide-induced rhabdomyosarcoma cultured for 59 passages maintained its heteroploid identity.(222) Nickel sulfide-induced rhabdomyosarcoma cells, embryonic muscle cells and differentiating muscle cells were compared. Nickel sulfide greatly affects the morphology and pattern of DNA synthesis in the embryonic, but not in the differentiating of tumor cells, indicating that the "normal" mitotic cells are affected either by interference with the cell membrane, intracellular enzyme systems, and/or nucleic acids. Although nickel sulfide drastically reduced the number of cells reaching mitotic S phase, the presence of a few cells that make it to S phase indicates that in vivo tumor induction involves the clonal proliferation of a few nickel-resistant cells.(223) Tumor cell mitochondria exhibit conformational changes, the accumulation of electron dense particles, and the elaboration of cristae which appears to coalesce and produce wavy or parallel stacks. Some enlargement and degenerative changes in the inner and outer mitochondrial membranes occurs, with replacement of cristae with 50-60 Å thick filaments. Similar changes are observed in normal rat muscle mitochondria after short exposure to nickel sulfide.(224) Administration of methandrostenolone to rats which had received a single injection of nickel sulfide in the gastrocnemius accelerated carcinogenic activity and increased tumor incidence from 33 to 100 per cent.(225) A synergistic carcinogenic effect was observed in rats treated with both intramuscular nickel sulfide and benzpyrene. The latency and mortality associated with tumors was as in Table 14.(226)

Table 14

Synergistic Carcinogenic Effects of Nickel and 3,4-Benzpyrene

Treatment	Average weeks to tumor	Weeks to death
Control	none	none
10 mg Ni_2S_3	26 ± 5	33 ± 5
5 mg 3, 4-benzpyrene	31 ± 10	41 ± 11
10 mg Ni_2S_3 + 5 mg 3,4-benzpyrene	18 ± 3	24 ± 5

C. Nonmammalian vertibrates

1. Birds

The growth of chicks up to four weeks of age was significantly depressed by the addition to the diet of 700 to 1300 ppm or more of nickel as the acetate or sulfate. Fat retention was not affected, but a reduction in nitrogen retention was observed with the higher nickel concentrations used.(176)

2. Fish

Nickel was detected in the bodies of fish killed by $NiSO_4$ solutions or nickel-plating solutions. Nickel was also detected in living fish in nickel solutions, but not in the bodies of normal fish.(159) Toxicities of mixtures of nickel, zinc, copper and phenal to the rainbow trout, Salmo gairdneri Richardson, could be adequately predicted by the summation of the toxicities of the individual poisons present.(227)

The bitterling(Rhodeus sericeus phoxinus), the carp (Cyprinus carpio L.) and the minnow (Phoxinus phoxinus) were observed to grow and develop normally in nickel concentrations of 0.1 mg per liter, the maximum admissible nickel concentration.(228) At alkaline pH's (8.0 or higher), nickel-cyanide complexes are less toxic to minnows (Pimephales promela) than cyanide alone due to the low degree of dissociation of the complex.(229)

D. Invertebrates

a. Toxicity

The maximum admissible nickel concentration of 0.1 mg per liter does not affect the normal growth and development of daphnia (Daphnia magna). A variable effect of the nickel concentration on the respiration rate of tubificid worms, (Tubifex tuifec and Limnodrilus hoffmeisteri) was observed as the pH was changed.(230)

b. Terratagenicity

Studies on the effects of nickel ion in solution on the development of two marine invertebrate species have been found. The concentration of nickelous ion at which 50% of the embryos of the American oyster, Crassostrea virginica, did not develop was 1.18 ppm.(231) The embryos and the fertilized eggs of the sea urchin, Lytechnicus pictus, take up radioactive nickel ions in the free state, which can be released by the addition of exogenous non-radioactive nickel ions. Embryos incubated in solutions containing 10^{-3} to 10^{-2}M nickelous ions cleaved at the normal rate and formed blastulas, but did not gastrulate. These embryos failed to develop dorsoventral symmetry and formed abnormal radialized larvae.(232)

E. Plants

Nickel toxicity in the oat, bean, pea, tomato and sunflower is manifested by a decrease in the cation exchange capacity of the roots.(170) The severity of the nickel toxicity in the oat plant is increased in the presence of abundant manganese. These two metals effect the increased uptake of iron into the plant, but inhibited iron metabolism inside.(233) Nickel sulfate added to the soil of Satsuma mandarin trees (2 gm per 30 cm diameter pot) suppressed tree growth, and increased amounts of nickel were observed in the twigs, leaves, large and fine roots. Soil and foliar applications of molybdenum reduced the effects of nickel, and tree growth was more vigorous.(234) In areas of the Phillipines with high nickel content soils, boang disease occurs, characterized by the production of empty or improperly fleshed nuts.(235)

In Chlorella grown in medium containing more than 0.5 gm nickel per liter, marked inhibition of growth and lowering of productivity occurred. These effects could be reversed by the addition of zinc or several other trace elements, disodium EDTA or an increase in suspension density.(236)

F. Microorganisms

Many examples of the toxicity of nickel salts to fungi which infect crops are presented under "Therapeutic Uses" and will not be reiterated here.

Both nickel and tin are toxic to wild type Aspergillus nidulans. K^+, NH_4^+, Mg^{++} and Ca^{++} can reverse the metal toxicities. Studies with a resistant mutant indicate that the resistance is due to an intracellular detoxification mechanism and not to reduced permeability to the metals.(237)

The toxicity of various metal salts, including nickel, to the fungus, Fusarium decemcellulare, can be reversed with sodium dimethyldithiocarbamate (DMDT).(238) Treatment of the conidia of F. decemcellulare with nickel salts (5 microgram Ni per ml for five hours) resulted in the excretion of various amino acids into the surrounding medium.(239)

The presence of nickel ions in the medium induces respiratory insufficiency in yeast.(240)

A study on the cytonarcotic action of nickel salts on Paramecium caudatum revealed that the time required for the protozoan to become motionless was proportional to the nickel concentration. The formation of digestive vacuoles decreases sensitivity to nickel narcosis, possibly because of associated decreases in cell membrane permeability. Twenty generations of ciliates must pass after nickel narcosis before multiplication becomes normal again. Different mating types have different sensitivities to nickel. The presence of Ba^{++} or Ca^{++} strongly antagonizes the effects of Ni^{++}.(241) The weakening of the ciliary apparatus of Paramecium by nickel is a step by step process, progressively excluding movements one by one in the order corresponding to their hydrodynamic effectiveness.(242) Solutions of nickel cause retraction of the axopodia of heliozoans much like treatment with colchicine or cold. Initially, a very fast axopodial shortening is observed, followed by a period of recovery, and then a slower retraction. Recovery from treatment is possible if exposure is not too long.(243)

The growth of Lactobacilli and Streptococci on agar plates is inhibited by nickel acetate and nickel-EDTA chelates in the medium.(158)

The addition of nickel salts to the medium induced abnormal inversed spiral movements in the ciliate, Paramecium multimicronucleatum.(244)

G. Results of Personal Contacts with Medical Personnel

A total of 74 toxicologists and medical examiners throughout the United States were contacted by telephone and letter with regard to professional acquaintance with accidental poisonings by nickel or nickel compounds. Of the 31 responses, one respondent had investigated the death of a child (age less than 5 years) who had ingested nickel chloride from a science project of an older sibling. This was the only positive response concerning nickel poisoning.

XI. STANDARDS

Nickel carbonyl

TLV: (recommended) 0.001 ppm in air (0.007 milligrams per cubic meter of air)(9)

Nickel and Nickel compounds

TLV: (recommended) 1 milligram per cubic meter of air.(9)

XII. SUMMARY AND CONCLUSIONS

A. Summary

Nickel is widely used in ferroalloys, stainless steels and metal plating. In steel alloys and as a plating material nickel offers superior corrosion resistance and excellent low-temperature porperties. Over 75 per cent of the nickel consumed yearly in the United States is imported; the domestic production (as ferronickel) occurs at Riddle, Oregon and amounts to about five per cent of the nickel consumption. The remainder, approximately 20 per cent of consumption, arises as a smelter byproduct (minor) or through recovery from scrap.

Nickel sulfate is the most important compound of nickel in commerce, and its primary use is in baths used for electroplating of nickel. Although much of the spent plating solution is recovered and used in nickel sulfate production, a significant amount of nickel waste (15 kkg Ni per year) arises from the electroplating industry. Nickel metal and nickel oxide are also used in nickel sulfate production. The waste effluents from nickel sulfate production are insignificant in comparison to other sources.

Of the estimated 4,895 metric tons per year of nickel entering the environment for the United States, over 90 per cent arises from the combustion of fuel oil and enters the atmosphere as oxides. The world-wide nickel content of the atmosphere began to increase during the 1920's and is continuing to increase.

Nickel carbonyl, a particularly toxic compound of nickel, may be formed by the reaction between nickel(in sewage sludge and other solid wastes) and hot carbon monoxide in incinerators and other combustion processes (carbon monoxide is formed when insufficient oxygen is available during combustion of carbonaceous materials). Such could occur in automobile engines when nickel is used as a fuel additive; such additives are currently banned in this country.

Toxic concentrations of nickel in soil and waters occur both naturally and as a result of man's activities in foreign countries (including Canada), but have not been reported to occur in the United States except as local effects of plating bath and similar effluents. Industrial and other occupational exposures have produced severe effects including deaths in other countries. Such hazards exist in this country, but reports of pathology other than dermatitis are few.

Many persons exhibit allergic reactions to nickel and nickel compounds. Several studies have indicated that two-thirds or more of female allergy patients exhibit sensitivity to nickel. The percentage for males is lower. The aqueous concentration of nickel at or below which no contact allergic reaction occurs in nickel-sensitive persons is one micromole of nickel per liter. Sensitivity to nickel often occurs concurrently with sensitivity to cobalt and chromium.

Various nickel compounds, particularly the sulfide and the carbonyl, are known carcinogens, and various environmental exposures to nickel in other countries seem to correlate with increased incidence of tumors in man. These include use of snuff made from tobacco grown on soil of high nickel content as well as occupational exposures.

Nickel is absorbed through the intestines, lungs and abraded skin. Urinary excretion is the principal mode of elimination of nickel. Nickel is present in both an ultrafiltrable and a protein-bound form in the blood. A dietary requirement for nickel has not been established. Nickel ions can replace calcium ions in the generation of action potentials in muscle, but the duration of the potential is increased.

Inorganic nickel salts are useful plant fungicides. Phytotoxicity occurs with excessive nickel levels. Nickel is absorbed by the plant through the roots. Plants grown on serpentine soils or industrial or mine waste heaps often have high nickel contents. Nickel ions inhibit growth of various microorganisms and produce a progressive narcosis in Paramecium.

B. Conclusions

The following conclusions are based on the information contained in this report:

(1) Nickel exhibits significant toxic effects toward man, other animals, plants and microorganisms.

(2) The most general toxic effect of nickel toward man involves widespread allergic sensitivity, but symptoms disappear when contact is avoided.

(3) Although nickel-containing industrial wastes are probably insignificant except on a very localized basis, the nickel content of petroleum has caused a continuing world-wide increase in atmospheric levels of nickel. This source of nickel could pose future health and environmental hazards if the increase continues.

(4) Under certain conditions involving the presence of both nickel and hot carbon monoxide, the very toxic nickel carbonyl can be formed in combustion processes.

C. Recommendations

The following recommendations are based on the summarized results and conclusions presented above:

(1) Allergic persons should be made aware of the high probability of their sensitivity to nickel (as well as other common metals).

(2) The future trend for atmospheric nickel content should be projected and compared to levels at which deleterious environmental or health would be expected in order to determine whether a future hazard from nickel might exist.

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